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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/091,578	10/06/1998	EDWIN L. MADISON	19191.0002	5096

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DAVID G PERRYMAN
NEEDLE & ROSENBERG
127 PEACHTREE STREET N E
SUITE 1200 THE CANDLER BUILDING
ATLANTA, GA 303031811

EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/091,578	Madison et al.
Examiner	**Art Unit**
Ron Schwadron, Ph.D.	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *13-65 and 67* is/are pending in the application.

4a) Of the above, claim(s) *25-64* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13-24, 65, and 67* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/29/2002 has been entered.

2. Claims 13-24,65,67 are under consideration. Claims 3 and 66 have been canceled. Claims 18-24,65 have been amended. Claim 67 is newly added.

3. The first line of the specification, page 1 needs to be amended to recite that the instant application is a 371 of PCT/US96/20577 filed December 19, 1996 and claims priority to US Provisional Application 60/009028 filed December 21, 1995.

4. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. The Patent Office now requires the submission of corrected drawings in response to an Office Action which includes a PTO-948 indicating that the drawings are defective. 37 CFR 1.85 states:

37 CFR 1.85. Corrections to drawings.
(a) A utility or plant application will not be placed on the files for examination until objections to the drawings have been corrected. Except as provided in § 1.215(c), any patent application publication will not include drawings filed after the application has been placed on the files for examination. ***Unless applicant is otherwise notified in an Office action, objections to the drawings in a utility or plant application will not be held in abeyance, and a request to hold objections to the drawings in abeyance will not be considered a bona fide attempt to advance the application to final action*** *(§ 1.135(c)). If a drawing in a design application meets the requirements of § 1.84(e), (f), and (g) and is suitable for reproduction, but is not otherwise in compliance with § 1.84, the drawing may be admitted for examination.*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the

subject matter which the applicant regards as his invention.

6. Claims 13-24,65,67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite in the recitation of "IgG-like" because it is unclear what this means or encompasses. Said term has no art recognized meaning and a definition of said term is not disclosed in the specification. Regarding applicants comments, if the term has an art recognized meaning then applicant should be able to provide art that defines what said term means.

Claims 22,23, 67 are indefinite in the recitation of "protein surface loop" because it is unclear what this means or encompasses. The specification, page 12, last paragraph defines said term in the context of a polypeptide of about 2 to about 20 amino acids which is a "flexible loop structure" with other specific properties. However, there is no definition of the term "flexible loop structure" in the specification and said term has no art recognized meaning. Therefore it is unclear as to what types of polypeptide of about 2 to about 20 amino acids would or would not constitute a flexible loop. For example, what properties would define a 2 or 3 amino peptide as a flexible loop versus nonflexible loop.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13-24,65,67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed molecule where the protein and exogenous protein surface loop are covalently linked, does not reasonably provide enablement for the claimed invention wherein the aforementioned molecules are noncovalently linked. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification is not enabling for scope of the claimed invention wherein the protein and exogenous protein surface loop are "linked" per se. The specification, page 14,

last paragraph discloses that "linked" encompasses noncovalent linkage. The specification is not enabling for the claimed invention which encompasses an exogenous protein surface loop noncovalently linked to a protein wherein the loop replaces an endogenous protein surface loop and has the functional properties recited in the claim, because there is no disclosure in the specification as to how such a molecule would be made. The specification discloses the production of covalently linked protein conjugates but provides no disclosure as to how to make a noncovalently linked version of the claimed invention. The prior art of record discloses a variety of methods for covalently linking two different molecules but does not disclose how an exogenous peptide could be substituted for a peptide in a molecule and attached via noncovalent linkage.

9. While the term "protein surface loop" is indefinite for the aforementioned reasons, for the purposes of prior art it will be interpreted as encompassing a ligand binding peptide or ligand binding region of a protein of about 2 to about 20 amino acids.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 67,13-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Mouritsen et al. (WO 95/05849) as evidenced by Van Ostade et al.

Mouritsen et al. disclose TNFα mutants wherein a T cell epitope was substituted into various regions of said molecule (see Example 3). The T cell epitope in the Example 3 replaces an endogenous protein surface loop on the protein (eg. the functionally active site in amino acids 26-35 of TNFa). It is an inherent property of the substitution that it replaces a region wherein said region mediates binding to TNF-R75 (see van Ostade et al.). While the term "protein surface loop" is indefinite, the region appears to have the same properties as the region disclosed in the example in the specification (eg. it is a ligand binding portion of a protein). The substituted exogenous surface protein loop consists of an optimized protein surface loop (eg. the epitope disclosed in page 10) that specifically binds a selected target protein on a cell (eg. T cells with the relevant TCR). TNFα is a cytokine.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 67,13-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (1993) in view of Mouritsen et al. (WO 95/05849)and Van Ostade et al.

Barbas et al. disclose Fab-9 wherein an optimized RGD peptide was inserted into CDR3 of said Fab (see pages 10004 and 10005). While the term "protein surface loop" is indefinite, the region appears to have the same properties as the region disclosed in the example in the specification (eg. it is a ligand binding portion of a protein). Barbas et al. teach that the inserted amino acid sequence mediates binding to the integrins recited in claims 20 and 21 wherein said integrins are cell surface proteins found on cells (see page 10006, first column). Barbas et al. do not teach that the molecule is one of the proteins recited in claim 67 or that the RGD molecule is substituted into an endogenous protein surface loop. Mouritsen et al. disclose TNFα mutants wherein a T cell epitope was substituted into various regions of said molecule (see Example 3). The T cell epitope in the Example 3 replaces an endogenous protein surface loop on the protein (eg. the functionally active site in amino acids 26-35 of TNFα). The substitution replaces a region wherein said region mediates binding to TNF-R75 (see van Ostade et al.) While the term "protein surface loop" is indefinite, the region appears to have the same properties as the region disclosed in the example in the specification (eg. it is a ligand binding portion of a protein). The substituted exogenous surface protein loop consists of an optimized protein surface loop (eg. the epitope disclosed in page 10) that specifically binds a selected target protein on a cell (eg. T cells with the relevant TCR). TNFα is a cytokine. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Barbas et al. teach the claimed invention except that the molecule is one of the proteins recited in claim 67 or that the RGD molecule is substituted into an endogenous protein surface loop, whilst Mouritsen et al. teach substitution of an exogenous binding moiety for a binding moiety of another molecule and that the substitution could be made into a cytokine or any other biologically

active molecule. One of ordinary skill in the art would have been motivated to do the aforementioned because Barbas et al. teaches that the RGD motif can be used to bind a biomolecule to an integrin and the role of integrins in a variety of disease states.

14. Claims 23,24,65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (1993) in view of Mouritsen et al. (WO 95/05849), Van Ostade et al. as applied to claims 67,13-22 above, and further in view of Anderson et al. (US Patent 5,262,170), Goeddel et al. and Bode et al.

The previous rejection renders obvious the claimed invention except for the limitations recited in claims 23,24 and 65. Bode et al. teach a modified plasminogen activator wherein a moiety to target said molecule to a platelet has been attached (see abstract) and potential uses for such a molecule (see abstract). Goeddel et al. teach tissue plasminogen activator (see abstract) and mutants of said molecule including multiple amino acid substitution mutants (see column 5, second paragraph). Anderson et al. teach that tissue plasminogen activator has a variety of ligand binding domains with specific functional characteristics (see column 2). Barbas et al. teach that Fab-9 contains a modified CDR3 which binds a β3 containing integrin found on platelets (see abstract, page 10003, second column, first incomplete paragraph). It would have been prima facie obvious to one of ordinary skill in that art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except for the limitations recited in claims 23,24 and 65, Mouritsen et al. teach substitution of an exogenous binding moiety for a binding moiety of another molecule, Anderson et al. teach that tissue plasminogen activator has a variety of ligand domains with specific functional characteristics, Goeddel et al. teach mutants of said molecule including multiple amino acid substitution mutants whilst Barbas et al. teach that Fab-9 contains a modified CDR3 which binds a β3 containing integrin found on platelets. A routineer would have used the CDR3 region from Fab-9 to target the tissue plasminogen activator to platelets. One of ordinary skill in the art would have been motivated to do the aforementioned because Bode et al. teach a modified plasminogen activator wherein a moiety to target said molecule to a platelet has been attached and potential uses for such a molecule while Barbas et al. teach that Fab-9 contains a modified CDR3 which binds a β3 containing integrin found on platelets and Mouritsen et al. teach substitution of an

exogenous binding moiety for a binding moiety of another molecule.

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644